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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,353	KRIEG ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-34 and 36* is/are pending in the application.

4a) Of the above claim(s) *30 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,29,31-33 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 6-12-08. Claims 28-34 and 36 are pending. Claims 1-27 and 35 have been cancelled. Claims 30 and 34 are withdrawn.

Claim Rejections Maintained

Double Patenting

2. The rejection of claims 28 and 36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 101, 107-109, 120-122, 124 of copending Application No. 10/314,578 are maintained for the reasons set forth in the previous office action.

Applicant arguments:

Applicants wish to make it clear on the record that the instant application and the cited patent application do not have common ownership, as common ownership is defined in MPEP 706.02(1). MPEP 706.02(1) states that the "term 'common ownership' means wholly owned by the same person(s) or organization(s) at the time the invention was made." Applicants also note that US 10/314,578 is a later filed application, which has now issued as US 7271156. Application of double patenting in a circumstance when the patents are not commonly owned and do not have identical inventorship and the claims under rejection have the earliest effective priority date would be contrary to the public policy reason for double patenting. The public policy behind the double patenting doctrine is to allow the public to freely use a patent upon its expiration. "The basic concept of double patenting is that the same invention cannot be patented more than once, which, if it happened, would result in a second patent which would expire some time after the original patent and extend the protection time wise." General Foods Corp. v. Studiengesellschaft Kohle MbH, (972 F.2d 1272, 1279, 23 USPQ2d 1839, 1844 (Fed. Cir.. 1992)). (See also In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993) and MPEP 804B). The instant application would not be expected to expire prior to

the expiration of the patent applications if they are to issue. Issuance of the instant patent application would not extend the patent protection beyond a point by which the public would otherwise be free to use the technology. Further US 7271156 which has an earliest effective priority date of September 25, 1999 is not prior art under any other section of the statute against the instant applicants or any other party that filed a patent application prior to 1999. To apply a double patenting rejection in the instant circumstance would extend beyond the purpose of the nonstatutory obviousness-type double patenting. Thus, double patenting is not appropriate in the instant circumstance. Applicants also call to the Exmainer's attention the existence of US 10/769282 which includes overlapping claims. Applicants have previously brought the existence of this patent application to the attention of the examiner and have submitted copies of Office Actions received in that case that were produced by a different examiner.

Examiner's Response to Applicant's Arguments:

Examiner disagrees with Applicant's assertion because the inventions do not have common ownership, this rejection would maintain as a obviousness-double-patenting rejection (see MPEP 804 Chart IIB). Although Applicants, stated that US 10/314,578 is a later filed application, which has now issued as US 7271156 does not share common ownership. However, US 10/314,578 is a later filed application, which has issued as US 7271156 and does share a common inventor with the present application therefore the rejection is maintained.

Claim Rejections Maintained - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. The rejection of claims 28-29, 31-33, and 36 under 35 U.S.C. 103(a) as being unpatentable over Kuramoto et al 1992 Jpn J. Cancer Res Vol. 83 pgs. 1128-1131 in view of Goodchild et al 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al US Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al US Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994) are maintained for the reason set forth in the previous office action.

4. The rejection of claims 28-29, 31-33, and 36 under 35 U.S.C. 103(a) as being unpatentable over Kataoka et al 1992 Jpn. J. Cancer Res. Vol. 83 pgs. 244-247 in view of Goodchild et al 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al US Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al US Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994)) are maintained for the reason set forth in the previous office action.

Applicant arguments:

Kuramoto et al described the use of 30-mer ODN having a particular 6 nucleotide palindromic sequence to induce IFN expression and enhance NK cell activation. A panel of ODN having different sequences and a phosphodiester backbone were tested for activity by incubation with mouse spleen cells. The authors hypothesize that the strong activity of bacterial DNA may be due to the palindromic sequences contained therein.

Kataoka et al. describe the use of palindrome-containing ODN for the treatment and prevention of tumors in mice. ODN were mixed with tumor cells and injected intradermally into mice. According to Kataoka et al. palindrome-containing ODN that were premixed with tumor cells suppressed tumor growth compared to ODN that did not include palindromes. Both the functional and nonfunctional ODN included a CG dinucleotide. Kataoka et al. also describe the production of a local immune reaction at the site of a tumor by injection of palindrome-containing ODN into the tumor lesion. They note that the antitumor activity of the ODN correlated well with NK and IFN activity.

According to the Examiner, Tokunaga et al. and Goodchild both teach backbone modifications. Applicants disagree regarding the teachings of Tokunaga et al. Tokunaga et al describe the synthesis of ODN "by the standard phosphoramidite method using a 0.2 tmol scale phenoxyacetyl support cassette" (page 56). The protocol described can either deliver a natural backbone or stabilized backbone ODN depending on the type of phosphoramidite monomer used in the coupling reactions and the type of oxidizer used in the oxidation reaction. A standard phenoxyacetyl-protected phosphoramidite monomer in the coupling step followed by oxidation with iodine would result in a non-stabilized natural backbone, while oxidation with a sulfurization reagent would produce a phosphorothioate ODN. Similarly, coupling of a 2'-O-methyl-modified phosphoramidite monomer followed by oxidation with either iodine or a sulfurization reagent would result in a stabilized backbone. However, Tokunaga et al. have only described a standard phenoxyacetyl protected assay, suggesting the production of a phosphodiester backbone ODN. There is no description of the use of a sulferization reagent or a 2'-O-methyl-modified phosphoramidite monomer.

The Examiner has indicated that Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA and that one of skill in the art would have been motivated to modify the ODN of Kataoka et al or Kuramoto et al. to include a backbone modification in order to improve stability or improve uptake Although it was known in the art that phosphorothioate backbone modifications increase stability of an oligonucleotide it was unknown whether phosphorothioate backbones should be used with immunostimulatory oligonucleotides. At the time of the invention is not clear how a change in backbone would affect the properties of the immunostimulatory oligonucleotides.

A 1993 Science paper by Stein et al (Science v. 261 p. 1004 1993) shows that phosphorothioate modifications can have unpredictable effects on an oligonucleotide. In fact, phosphorothioate can unpredictably redirect oligonucleotide activity to create biological activity against targets where there previously was none. Phosphorothioate modifications have many more biological effects than simply reducing oligonucleotide degradation in vivo. As detailed in Stein et al those effects were not well understood. For example, at p. 1008, col. 3 and p. 1009, cols. 1 and 2, four possible explanations for the non-specific antisense effects of a particular phosphorothioate antisense oligonucleotide are described. Additionally Perez et al. (PNAS v. 21, p.5597-5561, 1994) teaches that one should use caution when considering oligonucleotides with phosphorothioate backbones because of the danger of nuclear transcription factor induction.

Phosphate backbone modifications were known to have unpredictable effects on nucleic acids. Among the complications introduced by phosphorothioate modification is the creation of stereochemistry. The sulfur in a phosphorothioate modification introduces stereochemistry at each bond where it is present, creating distinct versions of the molecule. The two stereochemical forms of the phosphorothioate linkage each produce molecules with biological activities that can be distinct from each other, and distinct from an unmodified nucleic acid, having the same base pairs. Because stereochemistry is introduced at each site with a phosphorothioate bond, a molecule with several or many such bonds is actually an enormously complex mixture of different

chemical entities with unpredictable properties. This stereochemistry of phosphorothioates was known prior to 1994. One of skill in the art would not have known whether the introduction of stereochemistry would affect immunostimulation. This stereochemistry does not occur with the usual oxygen. In addition to the stereochemistry, the sulfur atom can have further effects on the activity of the nucleic acid simply due to its being much larger than the oxygen.

Those of ordinary skill in the art did not know the mechanisms through which the nucleic acids of Kataoka et al. or Kuramoto et al. achieved immune stimulation. Without knowledge of the mechanisms through which these nucleic acids achieved immune stimulation, it would have been unpredictable to one of ordinary skill in the art whether a phosphate backbone modification would totally destroy the immunostimulatory capability of the Kataoka or Kuramoto nucleic acids. In the absence of the work of the instant invention it would not have been known at the time of the invention whether a phosphorothioate bond or phosphorodithioate bond would substantially change the shape of the oligonucleotide so as to totally destroy immunostimulatory ability.

In Kataoka et al. or Kuramoto et al., there were palindromes that were inactive, therefore, even though Kataoka et al. or Kuramoto et al. attributed the "activity" of the oligonucleotides to palindromes, it would have been unclear to one of ordinary skill in the art what characteristics of the molecule were actually critical for activity. In the absence of the teachings of the invention, it would not have been predictable that a phosphate backbone modification to a molecule shown to be "active" in Kataoka et al. or Kuramoto et al would allow the molecule to retain its immune stimulatory effects.

Applicants disagree regarding the teachings of Hutcherson et al. Hutchison et al. does not disclose that the nucleic acids must have a CpG. While the 3 examples of oligonucleotides provided by Hutcherson et al. happen to contain a CpG, those examples do not include the oligonucleotides formulated in a delivery complex.

Hutcherson et al. does not teach one of skill in the art that a CpG is required or responsible for immunostimulation. In fact, Hutcherson et al. teaches that it is the phosphorothioate internucleotide linkage that has immunostimulatory activity.

Even if one of skill in the art would have combined the teachings of the references, Kataoka et al. or Kuramoto et al, Hutcherson et al., Tokunaga et al. Goodchild, and Cheng et al it would not have necessarily produced the claimed invention. Kataoka et al. teach that ODN having a hexameric palindromic motif are effective in reducing tumor size. Some of the functional ODN included a CG in the palindromic motif and others did not. All of the non-functional ODN which did not include palindromic motifs included a CG. One of skill in the art would not have been motivated based on these teachings to use an ODN comprising a 5'CG3' sequence to modulate an immune response. Thus, the claimed invention as a whole was not obvious in view of the combination of the four references.

Examiner's Response to Applicant's Arguments:

Applicant's arguments have been fully considered but are not deemed to be persuasive. Examiner accepts amendments that have been made to claims (1 and 11). Examiner understands the recent decision by the Supreme Court in KSR Int'l Co. v. Teleflex, Inc., No 04-1350 (U.S. Apr. 30, 2007). In response to applicant's arguments the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is why the references are combined under 35 U.S.C. § 103(a). Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The claims are drawn to an oligonucleotide, wherein each internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone modification is a phosphorothioate. Kuramato et al teach an oligonucleotide containing 5'-AACGTT-3'. Kuramoto et al teach that all oligonucleotide used were synthesized by the standard

phosphoramidite method using an automatic DNA synthesizer. As stated in the prior office action, Goodchild et al teaches an oligonucleotide wherein the phosphate backbone modification is a phosphorothioate (see pg. 167 column 1 last paragraph, column 2 last paragraph). Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA to enzymatic degradation (see pg. 167 "Synthesis of Modified Oligonucleotides", pg. 175 "The Effect of Modification on Nuclease Resistance"). Goodchild et al. teaches that shorter oligonucleotides are taken up more rapidly (see pg. 176 column 1 paragraph 5). Therefore, in regards to Applicant's assertion that Kuramoto et al hypothesize that the strong activity of bacterial DNA may be due to the palindromic sequences contained therein are is irrelevant, the limitations as claimed have been met.

It is noted that Applicant has listed several reference in the response to the present office action. In response to, Applicant's assertion that although it was known in the art that phosphorothioate backbone modifications increase stability of an oligonucleotide it was unknown whether phosphorothioate backbones should be used with immunostimulatory oligonucleotides and at the time of the invention is was not clear how a change in backbone would affect the properties of the immunostimulatory oligonucleotides; In response to Applicant's assertion that stereochemistry is introduced at each site with a phosphorothioate bond, a molecule with several or many such bonds is actually an enormously complex mixture of different chemical entities with unpredictable properties and that stereochemistry of phosphorothioates was known prior to 1994. In response to, Applicant's response of those of ordinary skill in the art did not know the mechanisms through which the nucleic acids of Kataoka et al. or Kuramoto et al. achieved immune stimulation and that without knowledge of the mechanisms through which these nucleic acids achieved immune stimulation, it would have been unpredictable to one of ordinary skill in the art whether a phosphate backbone modification would totally destroy the immunostimulatory capability of the Kataoka or Kuramoto nucleic acids.

Agrawal et al US Patent 5,194,428 before the invention was filed teaches phosphorothioate backbone modifications and that phosphorothioate backbones should

be used with immunostimulatory oligonucleotides. Agrawal et al teach a method of inhibiting influenza virus replication through the activity of modified oligonucleotides (oligodeoxynucleotides or oligoribonucleotides). Oligonucleotides (modified) which have antiviral activity against influenza virus as a result of their ability to hydridze to a selected region of influenza virus RNA and inhibit its ability to serve as a template for synthesis of encoded products, as well as compositions which include the oligonucleotides. Agrawal et al teach compositions having antiviral activity against influenza virus, which include the oligonucleotides of the present invention, and to a method of administering the oligonucleotides or compositions containing modified oligodeoxynucleotides to an individual for the purpose of inhibiting influenza virus replication (see Agrawal et al abstract claims, and in its entirety).

Furthermore, Hutcherson et al teach that phosphorothioate oligonucleotide analogs include at least one modified internucleotide linkage which, in addition to its enhancement of immune stimulation, can confer stability and enhance uptake of oligonucleotide into cells. An O (oxygen) of the phosphate diester group linking nucleotides is modified to S (sulfur). phosphorothioates often have in vivo half-lives over 24 hours and have been shown to be stable in cells, tissues, and drug formulations. Phosphorothioate oligonucleotide analogs are believed to enter cells by receptor-mediated endocytosis, and cellular uptake is often dependent on length and size, specific sequences, protein binding, and pendant modifications. Liposomes and cationic lipids can significantly enhance the uptake and fate of oligonucleotides and analogs (see line 20). Hutcherson et al further teach oligonucleotides containing a phosphodiester backbone were screened for anti-viral activity in an infectious yield assay and that the sequences showing the best activity in this assay were synthesized as phosphorothioate analogs, the phosphorothioate backbone modification greatly enhancing the antiviral activity of the oligonucleotides through stimulation of a local immune response.

Therefore based on the references as discussed above, it was known in the art that phosphorothioate backbones should be used with immunostimulatory

oligonucleotides and a change in backbone would affect the properties of the immunostimulatory oligonucleotides.

Applicant's assertion that although the 3 examples of oligonucleotides provided by Hutcherson et al. happen to contain a CpG, those examples are not including the oligonucleotides formulated in a delivery complex. Examiner disagrees, Hutcherson et al teach oligonucleotides as claimed and can be formulated in a delivery complex i.e. (liposomes see line 20) regardless of if the claim is used in the example of the prior art or not. Also, it one would have been motivated at the time the invention was made to incorporate an oligonucleotide in a delivery complex according to Hutcherson et al to because Hutcherson et al teaches that cationic lipids can significantly enhance the uptake and fate of oligonucleotides.

As to Applicant's response of Hutcherson et al. does not teach one of skill in the art that a CpG is required or responsible for immunostimulation. Examiner disagrees Hutcherson et al teach oligonucleotides in a method for stimulating a localized immune response. As stated before the claims are drawn to an oligonucleotide therefore it is irrelevant whether or not the CpG is required or responsible for immunostimulation.

Therefore the combined the teachings of the references, Kataoka et al. or Kuramoto et al, Hutcherson et al., Tokunaga et al. Goodchild, and Cheng et al it would have necessarily produced the claimed invention.

As outlined previously, the instant claims are drawn to an oligonucleotide, comprising: 5'-AACGTT-3', 8-40 nucleotides in length, wherein each internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate.

Kuramato et al teach an oligonucleotide, comprising: 5'-AACGTT-3', 8-40 nucleotides in length.

Kuramoto et al teach that all oligonucleotide used were synthesized by the standard phosphoramidite method using an automatic DNA synthesizer.

Kuramato et al does not teach an oligonucleotide wherein internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a

phosphorothioate, and having at least one phosphate backbone modification, wherein the oligonucleotide is linked to a nucleic acid delivery complex, wherein the oligonucleotide is covalently linked to the nucleic acid delivery complex, wherein the nucleic acid delivery complex is a cationic lipid, wherein the nucleic acid delivery complex is sterol. Kuramoto et al does not teach a composition of comprising the oligonucleotide and a pharmaceutically acceptable carrier.

Goodchild et al teaches an oligonucleotide wherein the phosphate backbone modification is a phosphorothioate (see pg. 167 column 1 last paragraph, column 2 last paragraph). Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA to enzymatic degradation (see pg. 167 "Synthesis of Modified Oligonucleotides", pg. 175 "The Effect of Modification on Nuclease Resistance"). Goodchild et al. teaches that shorter oligonucleotides are taken up more rapidly (see pg. 176 column 1 paragraph 5).

Hutcherson et al teach a composition (see column 5 lines 40-67, column 6 lines 31-43, column 7 lines 55-67, column 10 lines 46-57) comprising: an oligonucleotide delivery complex, wherein the oligonucleotide delivery complex contains an immunostimulatory CpG containing oligonucleotide associated (covalently) with a cationic lipid, wherein the CpG includes a phosphate backbone modification is a phosphorothioate (see abstract, column 5 lines 40-59, column 8 lines 31-50). Hutcherson et al teach a composition comprising a pharmaceutically acceptable carrier (see column 7 lines 49-55), wherein the oligonucleotide is synthetic (see column 8 lines 32-41).

Cheng et al teach oligonucleotides having phosphorothioate linkage covalently linked to a sterol.

It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Kuramato et al by modifying the backbone and inclusion of linking the oligonucleotide in a delivery complex according to Hutcherson et al to because Hutcherson et al teaches that cationic lipids can significantly enhance the uptake and fate of oligonucleotides. It would also have been prima facie obvious to modify the backbone of the oligonucleotide of Kataoka et al to include phosphorothioate

taught by Goodchild et al because Goodchild et al teaches that the backbone modifications prevent degradation by nucleases and increase or improve uptake (see section B pg. 167). It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Kuramoto et al by inclusion of a sterol because both Cheng et al and Kuramato both teach oligonucleotide in a delivery complex.

As outlined previously, the instant claims are drawn to an oligonucleotide, comprising: 5'-TGACGTT-3', 8-40 nucleotides in length, wherein each internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate.

Katoaka et al teach an oligonucleotide, comprising: 5'-TGACGTC-3' (BCG-A4a), 8-40 nucleotides in length.

Kataoka et al teaches that the oligonucleotide is synthesized by an automated DNA synthesizer and that the backbone is modified by the standard phosphoramiditie method as taught by Tokunaga et al. Tokunaga et al teach that the phosphate backbone modification is a phosphoramidite.

Katoaka et al does not teach an oligonucleotide wherein internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate, and having at least one phosphate backbone modification, wherein the oligonucleotide is linked to a nucleic acid delivery complex, wherein the oligonucleotide is covalently linked to the nucleic acid delivery complex, wherein the nucleic acid delivery complex is a cationic lipid, wherein the nucleic acid delivery complex is sterol. Kuramoto et al does not teach a composition of comprising the oligonucleotide and a pharmaceutically acceptable carrier.

Goodchild et al teaches an oligonucleotide wherein the phosphate backbone modification is a phosphorothioate (see pg. 167 column 1 last paragraph, column 2 last paragraph). Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA to enzymatic degradation (see pg. 167 “Synthesis of Modified Oligonucleotides”, pg. 175 “The Effect of Modification on Nuclease Resistance”).

Goodchild et al. teaches that shorter oligonucleotides are taken up more rapidly (see pg. 176 column 1 paragraph 5). Tokunaga et al. and Goodchild et al both teach backbone modifications.

Hutcherson et al teach a composition (see column 5 lines 40-67, column 6 lines 31-43, column 7 lines 55-67, column 10 lines 46-57) comprising: an oligonucleotide delivery complex, wherein the oligonucleotide delivery complex contains an immunostimulatory CpG containing oligonucleotide associated (covalently) with a cationic lipid, wherein the CpG includes a phosphate backbone modification is a phosphorothioate (see abstract, column 5 lines 40-59, column 8 lines 31-50). Hutcherson et al teach a composition comprising a pharmaceutically acceptable carrier (see column 7 lines 49-55), wherein the oligonucleotide is synthetic (see column 8 lines 32-41).

Cheng et al teach oligonucleotides having phosphorothioate linkage covalently linked to a sterol.

It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Katoaka et al by modifying the backbone and inclusion of linking the oligonucleotide in a delivery complex according to Hutcherson et al to because Hutcherson et al teaches that cationic lipids can significantly enhance the uptake and fate of oligonucleotides. It would also have been prima facie obvious to modify the backbone of the oligonucleotide of Kataoka et al to include phosphorothioate taught by Goodchild et al because Goodchild et al teaches that the backbone modifications prevent degradation by nucleases and increase or improve uptake (see section B pg. 167). It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Katoaka et al by inclusion of a sterol because both Cheng et al teach that oligonucleotide in a delivery complex show selective toxicity toward certain specific cancer cells, including some cancer cells which have multiple drug resistance (MDR) against certain established cancer chemotherapeutic agents.

Conclusion

Status of the Claims

4. No claims are allowed.

Claims 30 and 34 are withdrawn.

Claims 28-29, 31-33 and 36 are rejected.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisors, Shanon Foley can be reached on 571-272-0898 and Robert Mondesi at 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nina A Archie/
Examiner, Art Unit 1645
/N. A. A./
Examiner, Art Unit 1645

Nina A Archie
Examiner
GAU 1645
REM 3B31

/Mark Navarro/
Primary Examiner, Art Unit 1645